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# A prospective pilot study on early toxicity from a simultaneously intergrated boost technique for canine sinonasal tumours using image-guided intensity-modulated radiation therapy

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## 1 Zusammenfassung auf Englisch

In order to overcome the common local treatment failure of canine sinonasal tumors, integrated boost techniques were tried in the cobalt / orthovoltage era, but dismissed due to unacceptable early (acute) toxicity. Intriguingly, a recent calculation study of a simultaneously integrated boost (SIB) technique for sinonasal irradiation using intensity-modulated radiation therapy (IMRT) predicted theoretical feasibility. In this prospective pilot study we applied a commonly used protocol of 10x4.2Gy to the planning target volume (PTV) with a 20% SIB dose to the gross tumor volume (GTV). Our hypothesis expected this dose escalation to be clinically tolerable if applied with image-guided IMRT. We included nine dogs diagnosed with sinonasal tumors without local/distant metastases. For treatment planning, organs at risk were contoured according to strict anatomical guidelines. Planning volume extensions (GTV/CTV/PTV) were standardized to minimize interplanner variability. Treatments were applied with rigid patient positioning and verified daily with image-guidance. After radiation therapy, we set focus on early ophthalmologic complications as well as mucosal and cutaneous toxicity. Early toxicity was evaluated at week 1, 2, 3, 8, and 12 after radiotherapy. Only mild ophthalmologic complications were found. Three patients (33%) had self-limiting moderate to severe early toxicity (grade 3 mucositis), which was managed medically. No patient developed ulcerations/hemorrhage/necrosis of skin/mucosa. The SIB protocol applied with image-guided IMRT to treat canine sinonasal tumors led to clinically acceptable side effects. The suspected increased tumor control probability and the risk of late toxicity with the used dose escalation of 20% has to be further investigated.

## 2 Zusammenfassung auf Deutsch

Um die lokale Tumorkontrolle bei Nasenhöhlentumoren des Hundes zu verbessern, wurden in der Cobalt- / Orthovoltage-Ära spezielle Techniken mit intergrierter Boostdosis ausprobiert. Diese Techniken wurden aufgrund inakzeptabler akuter Strahlentoxizität abgelehnt. Eine theoretische Berechnung für die Durchführbarkeit eines simultan intergrierten Boost (SIB) zusammen mit Intensität-modulierten Strahlentherapie (IMRT) sagte eine akzeptable Toxizität voraus. In der hier beschriebenen prospektiven Studie wurde ein Standardprotokoll für Behandlung der Nasenhöhlentumoren 10x4.2Gy verabreicht und die Dosis im Tumorzentrum um 20% erhöht. Die Hypothese war, dass mit Hilfe der bildgeführte IMRT die Dosiserhöhung klinisch tolerabel ist und die Tiere keine starken Nebenwirkungen haben werden. Es wurden neun Patienten mit einem diagnostizierten Nasenhöhlentumor eingeschlossen. Die Behandlungen wurden mit hoher Präzision durchgeführt. Nach der RT wurde der Fokus auf Augenkomplikationen und akute Strahlentoxizität der Haut und Schleimhaut gelegt. Die akute Toxizität wurde in der Woche 1, 2, 3, 8, und 12 nach der RT evaluiert. Nur milde Augenkomplikationen konnten festgestellt werden. Drei Patienten (33%) hatten selbst-limitierende mittel- bis hochgradige akute Toxizität (Grad 3 Mukositis). Das intensivere SIB Protokoll, mit Hilfe bildgeführter IMRT für Behandlung von Nasenhöhlentumoren beim Hund hat klinisch akzeptable akute Nebenwirkungen gezeigt.

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ORIGINAL ARTICLE

# A prospective pilot study on early toxicity from a simultaneously integrated boost technique for canine sinonasal tumours using image-guided intensity-modulated radiation therapy

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In order to overcome the common local treatment failure of canine sinonasal tumours, integrated boost techniques were tried in the cobalt/orthovoltage era, but dismissed because of unacceptable early (acute) toxicity. Intriguingly, a recent calculation study of a simultaneously integrated boost (SIB) technique for sinonasal irradiation using intensity-modulated radiation therapy (IMRT) predicted theoretical feasibility. In this prospective pilot study we applied a commonly used protocol of 10 × 4.2 Gy to the planning target volume (PTV) with a 20%-SIB dose to the gross tumour volume (GTV). Our hypothesis expected this dose escalation to be clinically tolerable if applied with image-guided IMRT. We included 9 dogs diagnosed with sinonasal tumours without local/distant metastases. For treatment planning, organs at risk were contoured according to strict anatomical guidelines. Planning volume extensions (GTV/CTV/PTV) were standardized to minimize interplanner variability. Treatments were applied with rigid patient positioning and verified daily with image guidance. After radiation therapy, we set focus on early ophthalmologic complications as well as mucosal and cutaneous toxicity. Early toxicity was evaluated at week 1, 2, 3, 8 and 12 after radiotherapy. Only mild ophthalmologic complications were found. Three patients (33%) had self-limiting moderate to severe early toxicity (grade 3 mucositis) which was managed medically. No patient developed ulcerations/haemorrhage/necrosis of skin/mucosa. The SIB protocol applied with image-guided IMRT to treat canine sinonasal tumours led to clinically acceptable side effects. The suspected increased tumour control probability and the risk of late toxicity with the used dose escalation of 20% has to be further investigated.

**KEYWORDS**

boost, dog, IMRT, nasal, radiation, radiation toxicity, SIB, simultaneous, sinonasal, tumour

## 1 | INTRODUCTION

Radiation therapy (RT) is regarded as a standard of care treatment for canine sinonasal tumours; however, in spite of aggressive local treatment a definitive cure is rarely obtained. Median survival times with definitive-intent protocols applied in 10 to 18 fractions and total doses of 42 to 54 Gy are typically not exceeding 10.8 to 19.7 months.[1–9] The majority of patients, for example, 65% to 75%, have to expect local failure[2,3,6–10] and the progression-free interval in regularly fractionated protocols is short, with only 29% of dogs free of progression at 1 year.[7] In order to overcome the issue of poor local control, local treatment had been modified using post-radiotherapy surgical exenteration, 1 to 3 fraction stereotactic protocols or increased "boosts" of RT. Unfortunately, these modified treatments resulted only in either comparable[4,5,10] or only slightly better outcomes,[11] and in many cases also in unacceptable toxicity.[1,12]

The idea that with newer radiation technology a higher, more efficient dose can safely be given is intriguing. One way to increase radiation efficacy without delivering excessive dose to surrounding normal tissue, are shrinking field or boost techniques. With these

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techniques, a higher total dose is applied to the gross tumour volume (GTV, macroscopic tumour mass), while still giving the regular high dose to the clinical target volume (CTV, the possible area of tumour infiltration within nasal cavity and sinuses), as well as maintaining the fractionation effects.[6,12] More than 2 decades ago, a protocol with a boost technique was used to treat dogs with nasal tumours to a total dose of 57 Gy, but led to excessive radiation-related toxicity. Toxicity in early reacting tissues consisted of severe mucositis and dysphagia and was found unacceptable in 61% of the patients. Furthermore, median survival time was short and at least 35% of deaths were attributed to radiation-related early (acute) side effects.[12] Since then, only one study has described the use of a boost protocol for canine nasal tumours.[13] However, this study explored molecular imaging biomarkers and neither treatment planning details nor toxicity of radiation were reported. Outcome mentioned as a secondary endpoint with mean and median times to progression with 14.3 and 12.5 months, respectively.[13] No clinical trials reporting toxicity with boost techniques in dogs have been published since.

Especially in disease stages where the sinuses, orbit(s) and/or cribriform plate are invaded, the surrounding organs at risk (OAR) such as the eyes and brain can limit the available options to safely increase the radiation dose. However, conformal avoidance of OAR with a concurrent dramatic decrease of early and possibly late toxicity is nowadays possible with advanced treatment equipment and planning techniques, such as image-guided intensity-modulated radiation therapy (IG-IMRT).[7,14] Using the IMRT technique, a theoretical planning study quantified the risk in normal tissue and possible benefit in tumour control with an additional dose, added by means of a simultaneously integrated boost (SIB).[15] Boosting a selected subvolume within the tumour could be an ideal way to increase the tumour control probability (TCP) in tumours with poor local control. The TCP curve is of sigmoidal shape, and an additional 20% boost dose of radiation was predicted to lead to a large increase in tumour control in these canine patients (increasing from the current poor 29% to 74% at 1-year post-treatment).[15] Concurrently, because of the rapid dose-falloff outside the boost volume, reasonable patient safety in terms of normal tissue damage was predicted for this protocol. This protocol has not been implemented into clinical practice so far.

With this perspective and the broader future aim to improve local tumour control for sinonasal tumours in dogs, we clinically implemented a simultaneously integrated boost intensity-modulated radiation therapy (SIB-IMRT) protocol delivering a 20% increased dose to the GTV to assess tolerability as a first step. Our hypothesis was that the herein proposed 10-fraction protocol with a SIB used in this prospective pilot study will maintain an acceptable risk profile in terms of early radiation toxicity in dogs with sinonasal tumours.

## 2 | MATERIALS AND METHODS

### 2.1 | Patient and tumour characteristics

Dogs undergoing RT for malignant sinonasal neoplasia at the Division of Radiation Oncology, Vetsuisse Faculty, University of Zurich, Switzerland, were enrolled with owner consent in this prospective pilot study between January 2016 and March 2017. The patients are reported under a protocol approved by the Animal Ethics Council of the Canton of Zurich, Switzerland (*Permit Number: ZH075/17*). Staging workup to exclude regional and distant disease included fine-needle aspiration (FNA) of the regional lymph node (ipsilaterally or on the both sites), thoracic radiography and abdominal ultrasound, or total body computed tomography (CT). For treatment planning, a pre- and post-contrast standard CT scan of the tumour patient under general anaesthesia was performed with a 16 MDCT unit [Brilliance CT 16-slice, Philips Health Care Ltd, Best, the Netherlands] as previously described.[16] Tumour stage was established according to the modified Adam's staging system.[17] Biopsies were taken based on CT findings using a melon-ball forceps or via rhinoscopy. A baseline ophthalmic examination by a board-certified veterinary ophthalmologist (S.P.: DAVCO/DECVO or K.V.: DECVO) was performed prior to RT to ensure the absence of active ocular disease.

### 2.2 | Contouring of organs at risk and target volumes

Contouring of structures ("organs") at risk as well as tumour-related volumes was performed based on CT images. OAR were defined according to an anatomy textbook[18] and contoured as follows: (1) optical structures: (a) *Bulbus oculi*: eyeballs were contoured with a three-dimensional (3D)-contouring tool and diameter of the eyes was measured (usually 2-2.2 cm). In case of loss of symmetry and/or displacement of normal structures by tumour or tumour-associated changes, contouring was performed with a free-hand tool. (b) *Ocular lens*: contoured as a biconvex hyperdense structure, as distinguishable on pre- or post-contrast CT images.[19] (c) *Optic nerve*: defined including the nerve sheath and contoured from the posterior aspect of the globe, following its course through the orbit and optic canal in the sphenoid bone. The last slice was defined as the region where the optic nerve exits the optic canal in the sphenoid bone and enters the optic chiasm. Delineation was performed on post-contrast studies. (d) *Retina*: as previously described, the "retina-choroid-sclera complex" appeared as a single hyperdense curved line, bracketed by the rectus muscles and delineated from the posterior face of the vitreous chamber in pre-contrast studies.[20] (e) *Lacrimal gland*: the glands were contoured as visualized in contrast-enhanced CT images.[21] (2) Brain: The cranial, ventral, dorsal and lateral limits were represented by the bones forming the calvarium (*os frontale*, *os parietale*, *os occipitale*, *os sphenoidale* and *os ethmoidale*). The caudal end of the foramen magnum was represented by the caudal limit of the structure.[22] (3) Oral cavity: (a) Palate: the mucosal lining of the hard palate was contoured as imaged in a soft-tissue window (window level, 150 Hounsfield units [HU]; window width, 600 HU) (b) Tongue: the volume of the tongue was delineated as visible in the post-contrast images, caudally up to the first slice of the appearance of the laryngeal cartilages (keratohyoid cartilage). (4) Skin: it was extracted as 2 to 3 mm-thick wall from the body surface. The volume of interest (VOI) was set from rostral aspect of the nose to 2 cm caudally past the caudal border of the planning target volume (PTV). In the brachycephalic breeds, the skin contour was adapted manually. (5) Lymph nodes: they were not included into the treatment volume.

Tumour-related volumes were contoured as follows: the GTV was delineated using co-registered contrast-enhanced CT images and involved the contrast enhancing part of the tumour and the lytic bone as imaged in bone window (window level, 400 HU; window width, 1800 HU). The CTV accounting for subclinical microscopic disease extension was defined according to the institution's guidelines: (1) Frontal sinus: the whole sinusoid cavity was included into the CTV if filled with non-contrast enhancing soft tissue density (fluid or mucus) and/or if contrast enhancing soft-tissue (GTV) was present. (2) Nasal passages: in case of an intact nasal septum, only the affected nasal passage including fluid or air was included, with the contour maintained on the ipsilateral inside of the bone/septum. In case of bilateral disease and/or nasal septum destruction, both nasal cavities were included. In the slices where GTV was delineated, the CTV volume was extended 1 mm into the bone/nasal septum. In case of bone lysis, the margins were extended three-dimensionally into the soft tissue/adjacent bone and/or limited by non-involved compartments. The rostral and caudal limits of the CTV were chosen to be 2 cm from the GTV for sarcomas and 1.5 cm for carcinomas, or were caudally limited by bony structures. In a case of tumour extension outside the nasal cavity, the margins were extended three-dimensionally 2 cm from the GTV for sarcomas and 1.5 cm for carcinomas into the surrounding soft tissue and/or limited by non-involved compartments. In our institution all treatments are applied with rigid patient positioning devices and verified daily in an image-guided mode (IGRT). Therefore, the margin extension CTV-PTV was a 3D extension by 2 mm to define the PTV, accounting for systematic and random uncertainties. If the PTV extended past the body outline, it was automatically cropped to the body contour.

## 2.3 | Treatment planning

For treatment planning, the Eclipse External Beam Planning system version 10.0 (Varian Oncology Systems, Palo Alto, California) with the AAA-algorithm (10.0.28) was used. For the treatment planning CT, dogs were immobilized under general anaesthesia in an individually shaped vacuum cushion (BlueBag BodyFix, Elekta AB, Stockholm, Sweden) and a custom-made bite block.[23]

Treatment was planned with a SIB-IMRT technique. The SIB design intended to boost the GTV with a per-day additional dose of 20% ($EQD_2$) above the daily 4.2 Gy to the PTV.[15] Hence, the delivered plan included 2 different dose levels: 48.3 Gy to the GTV and 42.0 Gy to the PTV. Target coverage in the GTV was planned to be between 95% and 107% of the prescribed dose (45.9-51.7 Gy). For the PTV the minimal target coverage was 95% of the prescribed dose (39.9 Gy), with the maximum dose corresponding to the GTV boost (45.9-51.7 Gy). Tissue-equivalent Superflab pliable bolus of 1 cm thickness was placed in individual fields, if needed for adequate dose build-up. All measures for a steep dose-fall-off outside the GTV were taken and additional pseudo- or "helper"-structures (eg, a ring of 3 mm around the GTV) were created in order to reduce (1) conflicting inputs on dose constraints or (2) hot spots. Maximum doses with >110% of the prescribed doses were considered acceptable if limited to a small volume inside the PTV. Inverse planning using a dynamic multileaf collimator (MLC) with 5 mm leaf width was carried out with the priority to optimize target coverage and as a secondary goal to spare OAR. The doses to the OARs were kept as low as possible without compromising target volume coverage, but specific dose constraints were not applied.

Conformity index was calculated according to the formula: CI = $V_{95\%}$/TV, were $V95\%$ is the volume of 95% isodose line and TV is the volume of the target.[24] Homogeneity index was calculated according to HI = $(D_{2\%} - D_{98\%})/D_{50\%}$.[25] Because of the 2 different target volumes with different dose, conformity and homogeneity indexes were calculated for both GTV and PTV separately, and are listed in section 3 as mean ± SD. These calculations were performed retroactively and the plans were not evaluated for treatment according to these values.

Dose to OAR was reduced as much as possible during the optimization process. The dose to the targets was prescribed and documented in 2 ICRU reference points, which were defined as a representative point in the PTV on the 100% isodose line and in the GTV on the 100% SIB prescription isodose line. Recommendations for specification of dose were adhered to as proposed by the ICRU report 83.[25] According to the Swiss law and routine procedure in our clinic, each treatment plan was dosimetrically verified prior to treatment using an Octavius-Phantom (PTW Freiburg, Germany) and a medical physicist approved all treatment plans.

## 2.4 | Treatment delivery

The definitive-intent photon treatment of 10 × 4.2 Gy + 20% SIB (total dose: 42 Gy/SIB 48.3 Gy) was applied daily (workdays) over 2 consecutive weeks under general anaesthesia. Treatment was delivered with a 6 MV linear accelerator (Clinac iX, Varian, Palo Alto, California) with high accuracy and precision in target localization because of the abovementioned rigid patient positioning device. Daily image-guidance (IGRT) was used for treatment verification, using kV-kV orthogonal radiographs and/or kV cone-beam CT (CBCT). Therapy was delivered in a dynamic IMRT mode with isocentrically planned beams arranged in a coplanar manner.

## 2.5 | Permitted supportive care and assessment of early (acute) radiation toxicity

Owing to ethical reasons, all patients were allowed to receive the institution's standard supportive treatment for dogs undergoing RT for sinonasal tumours. Oral treatment with NSAIDs (Meloxicam 0.1 mg/kg SID [Metacam oral suspension for dogs 1.5 mg/mL, Boehringer Ingelheim, Germany]) was initiated in all patients at the time of diagnosis or immediately prior to the first radiation treatment. On the day of the first radiation treatment all patients were started on topical 0.2% cyclosporine eye ointment (Optimmune MSD Animal Health, Switzerland) and Vitamin A eye ointment (Vitamin A Blache, Bausch&Lomb, Berlin, Germany), applied to both eyes, twice daily. At the end of RT, a 3-week course of oral antibiotics (Amoxicillin clavulanate 20 mg/kg BID [Clavubactin 500/125 or 250/62.5, Graeub, Bern, Switzerland]) was initiated to prevent bacterial translocation at sites of radiation-induced mucosal or dermal barrier breach. In patients who exhibited severe cutaneous side effects and/or discomfort in the

first 3 weeks post-treatment, a switch from oral NSAID medication to oral prednisolone 0.5 mg/kg (Prednisolone, Streuli Pharma AG, Uznach, Switzerland) was permitted. In case of a change of medication from NSAIDs to prednisolone the patient was concurrently medicated with misoprostol 3 mcg/kg (Cytotec, Pfizer GmbH, Zurich, Switzerland) daily once for 3 consecutive days and omeprazol 1 mg/kg (Omeprazol, Helvepharm AG, Frauenfeld, Switzerland) twice daily, for 7 consecutive days. Antibiotic and anti-inflammatory medications were discontinued if the early side effects of radiation were healed at the 3-week recheck. Topical eye medications were discontinued at the 3-week recheck if Schirmer tear-test results were within our clinically recommended limits (eg, >15 mm/min).[26]

Patients were evaluated for radiation effects on early reacting tissues in the treatment field at the end of RT and 1, 2, 3, 8 and 12 weeks after completion of RT by a resident of the American College of Veterinary Radiology (Radiation Oncology) (ACVR-RO, A.S.), supported by an ACVR-RO diplomate (V.M., C.R.B.). Side effects were scored according to *Veterinary Radiation Therapy Oncology Group* (VRTOG) toxicity criteria.[27] Grade 3 toxicity (confluent mucositis) was defined as area of confluent mucositis larger than 2 cm in diameter or ulceration, haemorrhage and necrosis. A board-certified veterinary ophthalmologist evaluated the occurrence and severity of ocular side effects (S.P.: DAVCO/DECVO or K.V.: DECVO). Both examiners were unaware of the specific tumour stage, extent and laterality of the disease as well as the radiation dose distribution. Every patient received a standardized ophthalmic examination at the defined time points. The ophthalmic examination protocol included slit-lamp biomicroscopy using a hand-held slit lamp (Kowa SL-17) with ×10/16 magnification, indirect ophthalmoscopy using a Heine Omega 200 indirect ophthalmoscope with 20 and 28 diopter condensing lenses, Schirmer tear-testing (STT), Fluorescein and Rose Bengal staining, tear film break-up time (TFBUT) and corneal sensitivity estimation and applanation tonometry (measuring intraocular pressure, IOP) using a calibrated rebound tonometer (TonoVet) (see Appendix S1, Supporting information). A modified McDonald-Shadduck scoring system[28] was used to grade pathology in the anterior and posterior segment of the eye (see Appendix S2).

### 2.6 | Statistical analysis

Data were coded in excel and analysed with SPSS Version 24 (IBM Corp., Armonk, New York). Descriptive statistics such as absolute and relative frequencies as well as mean (median) and SD (IQR) were computed. The paired Wilcoxon test was used to compare the side effects at the various control points to the pre-treatment reference. The overall survival was defined as time from the first radiation treatment until death. The progression free interval (PFI) was defined as the time from the first radiation treatment until progression/recurrence of clinical signs confirmed by progressive tumour size in CT. There was a routine CT examination scheduled at 6 months recheck after RT. Progressive disease was defined as >20% increase in tumour volume according to RECIST criteria in solid tumours.[29] In both analyses, the cases were censored if lost follow-up or euthanized because of other cause and were derived from Kaplan-Meier tables. Differences were considered significant at *P*-values <.05. The follow-up was defined as the time from the first radiation treatment until lost to follow-up or death.

## 3 | RESULTS

### 3.1 | Patient population

Nine dogs (3 neutered males, 4 spayed females and 2 intact females) were included into this pilot study. The mean age at diagnosis was 10.2 ± 2.1 years (range: 8.0-13.9 years), and the mean body weight was 19.9 ± 9.8 kg (range: 9.9-33.4 kg). Breeds presented involved mixed breed dogs (*n* = 4), and 1 pure breed Beagle, Golden Retriever, Poitevin, French bulldog and Pug, each.

Mild age-related changes were present, but active ocular disease could be excluded in all dogs at the baseline ophthalmic examination prior to radiotherapy. Histopathological tumour examination was performed in 8 cases. In 1 patient, biopsy was forgone owing to a suspected bleeding disorder. The patients presented with adenocarcinoma (*n* = 2), esthesioneuroblastoma (*n* = 2), undifferentiated carcinoma (*n* = 1), undifferentiated sarcoma (*n* = 1), angiofibroma (*n* = 1) and in 1 case, the biopsy was not diagnostic. Fine needle aspirates of mandibular lymph nodes were performed bilaterally in 4 cases, ipsilateraly in 4 cases and were negative in all 8 cases. In the patient with angiofibroma, lymph nodes were not sampled. All patients were free of pulmonary metastases as staged with CT. Six tumours were localized in the left nasal cavity, 3 were localized in the right one. Hence, staging according to the modified Adams staging system revealed stage 4 in 3 cases (33.3%), stage 3 in 3 cases (33.3%), stage 2 in 2 cases (22.2%) and stage 1 in 1 case (11.1%). Mean tumour size (GTV) at treatment start was 22.8 ± 15.6 $cm^3$ (range: 3.9-43.9 $cm^3$) and the mean relative boost volume was 28.4% of the PTVs and ranged from 13.1% to 38.3% (Table 1).

### 3.2 | Treatment delivery

The mean doses to target volumes were within the aspired range with dose to GTV of 48.56 ± 0.29 Gy, to CTV of 45.96 ± 1.04 Gy and to PTV of 44.97 ± 0.88 Gy. The mean conformity index and the mean homogeneity index to GTV was 1.55 ± 0.25 and 0.07 ± 0.1, respectively. The mean conformity index and the mean homogeneity index to PTV was 1.33 ± 0.18 and 0.22 ± 0.04, respectively. All target volumes are listed in Tables 1 and 2, the doses to target volumes (including conformity and homogeneity indexes) in Table 2 and the doses to OAR in Table 3. Superflab pliable bolus was used in 3 cases total. In 1 case, it was used just in 1 field (0°), in 1 case in 2 fields (20° and 340°) and in 1 case in 3 fields (0°, 72°, 288°).

### 3.3 | Radiation toxicity

Mild to moderate early effects of radiation were seen in all cases as provided in Table 4. These side effects were managed with the provided supportive care. One patient was switched from non-steroidal drugs to steroid medication, 1 patient who was already on a low dose of prednisolone therapy for unrelated reasons was maintained on steroids and 1 patient received additional opioid pain medication

**TABLE 1** Target volumes and recorded highest grade and location of early toxicity

| Patient | GTV ($cm^3$) | CTV ($cm^3$) | PTV ($cm^3$) | Relative boost volume (%) | Disease stage | Highest grade of toxicity | Location of highest toxicity | No. of weeks post-RT |
|---|---|---|---|---|---|---|---|---|
| 1 | 43.9 | 75.3 | 114.7 | 38.3 | 4 | 1 | Mucosa | 1 |
| 2 | 6.3 | 10.1 | 18.9 | 33.3 | 4 | 3 | Mucosa | 1 |
| 3 | 3.9 | 19.6 | 29.7 | 13.1 | 1 | 1 | Mucosa, skin | 1 |
| 4 | 43.3 | 82.2 | 114.1 | 38.0 | 2 | 2 | Mucosa | 2 |
| 5 | 22.9 | 53.9 | 78.4 | 29.2 | 3 | 3 | Mucosa | 0 |
| 6 | 12.2 | 65.0 | 92.8 | 13.1 | 4 | 1 | Skin | 1 |
| 7 | 20.5 | 56.8 | 83.0 | 24.7 | 2 | 3 | Mucosa | 1 |
| 8 | 13.8 | 27.0 | 43.2 | 32.0 | 3 | 2 | Mucosa | 2 |
| 9 | 38.7 | 86.7 | 115.2 | 33.6 | 3 | 1[a] | Skin[a] | 1[a] |

Abbreviations: CTV, clinical target volume; GTV, gross tumour volume; PTV, planning target volume; RT, radiation therapy.

[a] Evaluated by referring veterinarian.

**TABLE 2** Mean volumes and doses for target volumes, dose conformity and homogeneity indices

| | Mean volume (mean ± SD) ($cm^3$) | D2% (mean ± SD) (Gy) | D50% (mean ± SD) (Gy) | D98% (mean ± SD) (Gy) | Conformity index (mean ± SD) | Homogeneity index (mean ± SD) |
|---|---|---|---|---|---|---|
| GTV | 22.83 ± 15.60 | 49.79 ± 0.37 | 48.56 ± 0.29 | 46.42 ± 1.40 | 1.55 ± 0.25 | 0.07 ± 0.1 |
| CTV | 52.96 ± 28.01 | n.a. | 45.96 ± 1.04 | 45.96 ± 1.04 | n.a. | n.a. |
| PTV | 76.67 ± 37.58 | 49.57 ± 0.35 | 44.97 ± 0.88 | 39.68 ± 1.51 | 1.33 ± 0.18 | 0.22 ± 0.04 |

Abbreviations: CTV, clinical target volume; GTV, gross tumour volume; PTV, planning target volume.

**TABLE 3** Mean volumes and doses for organs at risk

| | Mean volume (mean ± SD) ($cm^3$) | D2% (mean ± SD) (Gy) | D33% (mean ± SD) (Gy) | D50% (mean ± SD) (Gy) | D66% (mean ± SD) (Gy) | D98% (mean ± SD) (Gy) |
|---|---|---|---|---|---|---|
| Eye ipsilateral | 5.40 ± 0.95 | 33.30 ± 5.63 | 20.15 ± 6.32 | 17.60 ± 6.12 | 15.64 ± 6.01 | 11.51 ± 5.56 |
| Eye contralateral | 5.52 ± 0.84 | 23.77 ± 7.85 | 16.35 ± 5.28 | 14.50 ± 5.22 | 13.11 ± 5.28 | 8.92 ± 4.81 |
| Lens ipsilateral | 0.47 ± 0.09 | 18.98 ± 5.95 | 16.43 ± 6.72 | 14.80 ± 5.65 | 14.13 ± 5.68 | 9.21 ± 7.68 |
| Lens contralateral | 0.46 ± 0.10 | 18.71 ± 5.94 | 16.11 ± 5.98 | 15.32 ± 5.96 | 14.59 ± 5.92 | 13.82 ± 6.70 |
| Retina ipsilateral | 1.11 ± 0.35 | 38.54 ± 3.76 | 27.46 ± 6.00 | 23.34 ± 6.69 | 20.48 ± 6.98 | 11.13 ± 9.20 |
| Retina contralateral | 1.08 ± 0.38 | 24.84 ± 9.73 | 16.59 ± 6.10 | 14.42 ± 5.70 | 12.75 ± 5.45 | 5.08 ± 4.75 |
| Lacrimal gland ipsilateral | 0.18 ± 0.09 | 21.17 ± 10.13 | 18.56 ± 9.58 | 17.80 ± 9.22 | 17.06 ± 8.83 | 13.60 ± 9.24 |
| Lacrimal gland contralateral | 0.18 ± 0.07 | 13.62 ± 5.82 | 11.07 ± 5.17 | 10.32 ± 5.18 | 9.44 ± 5.10 | 6.20 ± 5.83 |
| Optic nerve ipsilateral | 0.30 ± 0.09 | 36.28 ± 5.91 | 31.22 ± 8.95 | 28.32 ± 10.80 | 24.43 ± 13.45 | 5.73 ± 8.63 |
| Optic nerve contralateral | 0.23 ± 0.09 | 23.95 ± 12.15 | 20.04 ± 10.54 | 18.76 ± 10.09 | 16.65 ± 10.58 | 8.43 ± 10.29 |
| Brain | 83.51 ± 4.27 | 34.36 ± 5.97 | 6.73 ± 6.15 | 2.41 ± 2.48 | 0.84 ± 0.46 | 0.39 ± 0.17 |
| Tongue | 80.72 ± 35.47 | 19.57 ± 5.02 | 11.35 ± 4.11 | 9.02 ± 3.68 | 6.17 ± 3.58 | 0.77 ± 0.41 |
| Palate | 6.51 ± 2.81 | 44.84 ± 4.65 | 38.96 ± 6.26 | 36.21 ± 7.07 | 30.68 ± 12.52 | 14.84 ± 12.73 |
| Skin | 60.95 ± 22.16 | 36.22 ± 5.75 | 16.58 ± 6.00 | 10.67 ± 4.42 | 6.07 ± 3.92 | 0.67 ± 0.26 |

tramadol-hydrochloride 2 mg/kg every 8 hours (Tramadol-Mepha, Mepha Parma AG, Switzerland) in the second week post-RT because of suspected pain and discomfort. None of the 3 patients with grade 3 mucosal side effects showed ulceration, mucosal bleeding or necrosis at any time after treatment. The most severe side effects were observed in the oral mucosa (lip). Ocular changes as found in the repeated ophthalmic examinations were clinically negligible. One dog developed mild blepharitis 3 weeks after radiation because of dry desquamation surrounding the eyes which resolved completely on the following recheck. The values of IOP and STT are listed in Table 5. In spite of a numerical significant decrease of IOP in the contralateral eyes 1 week after radiation ($P$ = .038), significant increase in STT 1 week after radiation on the contralateral side ($P$ = .018) and significant decrease in STT 2 weeks after radiation on the ipsilateral side ($P$ = .028), the values remained within the reference ranges and did not affect the patients clinically. The TFBUT values were somewhat reduced at various time points after radiation but no other signs of tear film instability were observed. Mild peripheral corneal (max 2-3 mm from limbus) and peripheral conjunctival pigmentation was observed after irradiation of both eyes in 6 patients. This pigmentation remained stable or decreased at later time points in all 6 cases.

Although late effects were not a primary endpoint in this study, the following observations were made in dogs followed longer than 12-weeks post-treatment ($n$ = 7 ≥6 months, $n$ = 6 ≥9 months, $n$ = 4

**TABLE 4** Grades of early side effects over time, according to the VRTOG acute radiation morbidity scoring scheme criteria[27]

| VRTOG criteria | Grade | End of RT ($n$ = 9) | 1 Week post-RT ($n$ = 9) | 2 Weeks post-RT ($n$ = 9) | 3 Weeks post-RT ($n$ = 9) | 8 Weeks post-RT ($n$ = 7) | 12 Weeks post-RT ($n$ = 7) |
|---|---|---|---|---|---|---|---|
| Mucosa | 0 | 6 | 2 | 2 | 8 | 7 | 7 |
| | 1 | 1 | 4 | 2 | 1 | 0 | 0 |
| | 2 | 1 | 1 | 5 | 0 | 0 | 0 |
| | 3 | 1 | 2 | 0 | 0 | 0 | 0 |
| Skin | 0 | 6 | 3 | 2 | 4 | 4 | 4 |
| | 1 | 2 | 5 | 6 | 5 | 3 | 3 |
| | 2 | 1 | 1 | 1 | 0 | 0 | 0 |
| | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Eye ipsilateral | 0 | 9 | 9 | 7 | 7 | 7 | 7 |
| | 1 | 0 | 0 | 2 | 2 | 0 | 0 |
| | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Eye contralateral | 0 | 9 | 9 | 8 | 6 | 7 | 7 |
| | 1 | 0 | 0 | 1 | 3 | 0 | 0 |
| | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 | 0 | 0 | 0 | 0 | 0 | 0 |

≥12 months, $n$ = 2 ≥18 months): Cataracts were observed in 6 dogs in both eyes at baseline examination and were classified as age-related because of clinical appearance with multifocal punctate nuclear and/or cortical and spoke or wedge-like cortical cataracts.[30] These cataracts were stationary in 4 cases, in one case progressed slowly on the ipsilateral side at the 2 months recheck and in one case progressed bilaterally at later time points (6 and 9 months). A nuclear purverulent/glasswool cataract was observed in 1 eye of 1 dog at the baseline ophthalmologic examination and did not progress at later time points. Furthermore, one of the dogs developed focal punctate retinal haemorrhages on the tumour-ipsilateral side after 2 months, which might be attributed to radiation toxicity. This change was initially very slowly progressive over time (at 3, 6 and 9 months) including focal retinal degeneration and bullous detachment. At 6 months a mild haemorrhage was also noted in the retina of the other eye, but vision did not seem to be affected at any time. Surprisingly, at 12 months, the retinal changes were regressive in nature.

### 3.4 | Survival analysis and follow-up

The mean follow-up was 280 days, median was 289 days (95% CI: 141-420 days). One dog was euthanized because of a pre-existing laryngeal paralysis 1.5 months after the end of RT, and 1 dog was lost to follow-up between week 3 and week 7 (Tables 4 and 5). For progression-free interval, the median was not reached during the observation time. The mean PFI was 372 days (95% CI: 280-464 days). All dogs were re-imaged with CT at the time of recurrence or progression of clinical signs. No patient (sufficient follow-up in 7 cases) was progressive on routine CT examination 6 months after radiation without having recurrence or progression of clinical sings acutely. The mean survival time was 450 days (95% CI: 305-597 days), median survival time again not reached. During the time of observation, no severe toxicity on late reacting tissues was seen.

## 4 | DISCUSSION

The use of IMRT compared to the very basic 2D planning of former decades has been shown to severely reduce frequency and severity of toxicity to the OAR in sinonasal tumour patients.[7] However, while IMRT planning by itself can achieve a higher conformity of dose to the PTV, the key to taking maximum advantage of this technique is to minimize the PTV-expansion margin. The reduction of this technical, not patient-given expansion margin will effectively reduce the (normal tissue) volume receiving high doses and is readily achieved with accurate treatment setup such as rigid head fixation,[23,31] and/or daily image verification.[7,32] The physical dose parameters (Table 2) in our study showed a good homogeneity, close to 0 (a HI of 0 indicates that the absorbed dose-distribution is almost homogenous).[25] The conformity indices in GTV and PTV were slightly higher than

**TABLE 5** Values of the ophthalmological examinations (mean ± SD)

| | | Basal examination ($n$ = 9) | End of RT ($n$ = 9) | 1 Week post-RT ($n$ = 9) | 2 Weeks post-RT ($n$ = 9) | 3 Weeks post-RT ($n$ = 9) | 8 Weeks post-RT ($n$ = 7) | 12 Weeks post-RT ($n$ = 7) |
|---|---|---|---|---|---|---|---|---|
| STT (mm/min) | Eye ipsilateral | 24.1 ± 3.7 | 23.0 ± 5.4 | 26.3 ± 5.7 | 21.0 ± 2.7 | 22.9 ± 3.8 | 19.7 ± 3.1 | 20.5 ± 3.6 |
| | Eye contralateral | 22.4 ± 5.9 | 22.8 ± 5.2 | 26.6 ± 5.2 | 22.8 ± 3.0 | 23.9 ± 6.0 | 20.2 ± 2.2 | 20.2 ± 4.9 |
| IOP (mm Hg) | Eye ipsilateral | 14.3 ± 5.6 | 10.3 ± 2.8 | 10.1 ± 3.9 | 12.3 ± 5.4 | 13.6 ± 4.2 | 14.0 ± 3.8 | 16.5 ± 2.9 |
| | Eye contralateral | 14.3 ± 5.4 | 12.2 ± 3.9 | 10.3 ± 3.1 | 12.8 ± 6.1 | 14.5 ± 3.6 | 15.8 ± 4.2 | 15.8 ± 3.7 |

Abbreviations: IOP, intraocular pressure; RT, radiation therapy; STT, Schirmer tear-testing.

1, indicating that the irradiated volume slightly exceeds the target volume and covers part of the healthy tissue. However, by maintaining D2% and D98% for regions of high and low absorbed dose, respectively, a CI >1 indicates a high plan normalization. Usually, a treatment is considered in accordance with the protocol if the conformity index is between 1 and 2.[24]

However, the use of IMRT with the commonly used definitive-intent protocols was neither expected nor found to increase tumour control per se.[7,33] An increase in local tumour control necessitates a higher radiation dose. While one possibility of increasing the dose by using the even more conformal proton therapy was described,[34] this treatment is hardly available for animal patients and outcome with an escalated dose was never tested. Hence, to increase the dose to the tumour, the suggestion and theoretical feasibility calculation to use a SIB with IG-IMRT[15] was used in this pilot study. The focus of the herein described pilot population was to evaluate in a first step, that the acceptable risk profile in terms of early radiation toxicity using a 20% SIB with IG-IMRT is clinically reproducible.

In prior trials delivering 42 Gy in 10 fractions with minor conformality, strong mucositis (grade 3) was found in 67% of dogs after 2 weeks, persisting >4 weeks in 38% of the patients.[1,2] In contrast, the same protocol applied with IG-IMRT (tomotherapy) only showed mucositis limited to grade 1 and 2 mucositis that resolved by 2 weeks after RT in all dogs.[7] As expected, the early toxicity in our study was slightly higher, with grade 3 confluent mucositis seen in 3/9 dogs (33%) at the end, 1 and/or 2 weeks after RT (Table 4). However, the differentiation between patchy and confluent mucositis is gradual and not clearly specified in the VRTOG acute radiation morbidity scoring scheme and our herein used definition of grade 3 confluent mucositis (area of mucositis >2 cm in diameter) might overstate the observed toxicity. The side effects resolved rapidly and by 3 weeks post-RT, all side effects had healed to ≤grade 1 toxicity score. The mean doses to the eyes were about 5% higher than described with a non-boost protocol[7] with 17.6 Gy (±6.1 Gy) in the eye ipsilateral to the tumour and 14.5 Gy (±5.2 Gy) in the contralateral eye. The ophthalmic specialists' findings were limited to mild changes in corneal pigmentation, IOP, tear production and TFBUT. Nevertheless, clinically the eyes remained fully functional, comfortable and grossly normal to the owners as well as the attending veterinarian. The supportive care prescribed to all patients enrolled in the study has the potential to reduce side effects in all early reacting tissues, including the eyes. Although late effects were not routinely evaluated in this study, the observed cataract progression in 2 dogs and retinal haemorrhages in 1 dog with longer follow-up periods underline the fact that a follow-up study aimed at investigating the late effects of this irradiation protocol is warranted. Cataract development is a typical late side effect of radiation observed already after a single dose of 2 Gy or a larger dose of 5 to 8 Gy for a prolonged or fractionated exposure. The latent period of cataract development is several years and it decreases with increasing dose.[35] The latency of cataract development was 6 to 12 months in dogs in one study, but the dose to the lens in not reported specifically.[36]

During our study period, the observed cataracts were stable or slowly progressive corresponding to both the suspected age-related nature and reaction to radiation. However, the study period was too short to evaluate these late side effects. The progressive retinal bleeding observed clinically in 1 patient after 2 months (a late side effect as well) has also been described in a small number of patients (2/14) treated with 42 Gy in 10 fractions on post mortem globe evaluation[7] and in a larger series of dogs treated with various less conformal protocols and total doses of 36 to 67.5 Gy.[36] In these published cases, both clinically and histologically identified retinal haemorrhages appeared at similar time points—3 to 6 months post-RT.[36]

Currently, various efforts are undertaken to overcome the poor local tumour control in canine sinonasal tumours. The use of concurrent chemotherapy/radiation potentiators seems only justified if specific and selective tumour (and hence not normal tissue) sensitization can be guaranteed. However, previous efforts with implantable low-dose releasing cisplatinum-containing implantable sponges could not demonstrate tumour selectivity in terms of improved local control.[37,38] Similar outcomes have been reached by groups using high conformality as applied in stereotactic techniques (stereotactic body radiation therapy [SBRT], stereotactic radiosurgery [SRT]).[4,5,11] The use of stereotactic, severely hypofractionated radiation regimes in general prescribe the dose to a GTV/PTV volume, which is smaller than the commonly used GTV/CTV/PTV setup of conventional RT.[4,5] While it indeed can be argued that most cases treated with more finely fractionated protocols progress from the original GTV rather than from the microscopic disease in the CTV[1,2,7,8,15] (and hence the volumes other than GTV are of lesser importance), future increased local control could again shift this paradigm. In the authors' view, canine sinonasal tumours need to remain considered as disease of infiltrative nature and usually large extent, which do not primarily qualify for SRT/SBRT. Furthermore, the SRT/SBRT regimes fully or partially forgo the positive effects of fractionation, such as reoxygenation and potentially massively increase the risk of late toxicity, especially when applied to larger volumes.

As predicted by the theoretical approach to estimate early toxicity for a standard treatment protocol with a 20% SIB for canine sinonasal tumours, the early ocular, mucosal and cutaneous toxicities observed in this prospective clinical pilot study were in a tolerable range in terms of occurrence and severity.[15] The cases selected for this approach represent a regular cross-section of clinical presentations, as all stages of disease were included. Mean relative boost volume in our study was larger than in the theoretical planning study (28.5% vs 9.7%,[15] respectively). However, the absolute boost volumes (GTV) were comparable in both studies, with our study having smaller PTVs, probably caused by the small technical, not patient-given expansion margin from CTV to PTV. Hence, the SIB protocol applied with IG-IMRT at our institution led to clinically acceptable side effects and represents a novelty in the treatment of canine sinonasal tumours.

We acknowledge limitations of the results presented herein which should direct future research approaches. The case number was limited to a small group of patients without randomized assignment, 2 dogs were not definitely diagnosed and 1 dog had an uncommon tumour type (angiofibroma). To assess the true levels of early side effects and—more importantly—the potential benefit in outcome and the relative late toxicities, future results should be collected adhering to evidence-based principles in prospective, randomized

clinical trials. Early (acute) toxicities even of higher grades should in general not be considered a treatment-limiting factor, as long as they are self-limiting and clinically manageable with symptomatic support. However, because of the prior reported sombre outcomes due to very strong early side effects in a study using a boost protocol,[12] we decided to perform a pilot study with a preliminary focus on early side effects. In parallel to local tumour control, potential late toxicities must constitute the more important focus for the future. Especially in advanced disease settings (eg, stage IV tumours), boost protocols might deliver high doses to parts of fraction-sensitive tissues such as brain, causing severe late radiation toxicity.

In conclusion, our findings suggest that a 20% SIB-enhanced radiation protocol can safely be applied to canine sinonasal tumours with acceptable early side effects to ocular, mucosal and cutaneous structures. The use of SIB-enhanced radiation protocols may offer a future route to improve the poor local tumour control in dogs with sinonasal tumours without causing excessive discomfort to the patient or even loss of functionality in OAR after treatment.

## Conflict of interest

The authors declare no potential conflict of interests.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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